

# Oxidative Metabolism in Fetal Rat Brain During Maternal Halothane Anesthesia

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The present study examines the effects of maternally administered halothane on fetal brain metabolism as determined by direct tissue analysis. Term pregnant rats were paralyzed, ventilated, and administered halothane in concentrations of 0.4, 1, or 2%. For comparison of fetal responses to anesthetic agents, other maternal rats were administered pentobarbital (50 or 200 mg/kg). Dams receiving 0.4% halothane or 50 mg/kg pentobarbital remained normotensive, whereas 2% halothane or 200 mg/kg pentobarbital led to a 65% reduction in maternal blood pressure and a 3-fold increase in blood lactate. Fetal blood lactate tended to parallel the maternal lactacidemia. Fetuses of dams anesthetized with 0.4% halothane or 50 mg/kg pentobarbital exhibited concentrations of cerebral metabolites comparable to those of control animals. A 2% halothane level was associated with metabolic disturbances in fetal brain, indicative of cerebral hypoxia. Pentobarbital 200 mg/kg, although producing maternal hypotension and lactacidemia to a degree similar to 2% halothane, preserved a more optimal fetal cerebral energy state as reflected in a lower lactate/pyruvate ratio and normal ATP. The metabolic influence of pentobarbital may serve to protect the hypoxic fetus from neurological damage, an effect apparently not shared by maternally administered halothane.

## Introduction

Modern obstetrical practice attempts to combine safe delivery of the fetus with maximum comfort for the mother. Achievement of this goal requires judicious use of medications which produce maternal analgesia without affecting the fetus. Unfortunately, all current analgesics and anesthetics can affect fetal homeostasis with possible deleterious consequences during and following birth. Included among the obstetrical anesthetic agents is halothane, which is known to exert physiological and biochemical effects on multiple organ systems, and by these actions indirectly affect fetal metabolism (1, 2). In addition, halothane, by nature of its low molecular weight and lipid solubility, readily diffuses across the placenta (3). Upon entering the fetal circulation, the agent is widely distributed to have major influences upon fetal cardiovascular and cerebral function.

Previous studies of maternally administered anesthetics have focused on disturbances in fetal acid-base status and cardiovascular hemodynamics, but little attention was paid to pos-

sible alterations in cerebral metabolism. Hence, the present investigation emphasizes the cerebral metabolic responses of fetuses whose dams were subjected to various concentrations of halothane. During anesthesia, measurements of maternal blood pressure and acid-base balance were correlated with fetal oxidative metabolism and the energy state of the brain. For comparison, cerebral metabolism in fetuses of pentobarbital anesthetized dams also was investigated.

## Methods

Term pregnant rats were anesthetized with ether, tracheostomized, and paralyzed with tubocurarine (3 mg/kg). Animals were artificially ventilated with 70% nitrous oxide and 30% oxygen ( $N_2O-O_2$ ) by means of a Harvard rodent respirator which was adjusted to maintain normal arterial blood gas and acid-base balance ( $pH_a = 7.35-7.41$ ;  $PaCO_2 = 35-40$  mm Hg;  $PaO_2 > 85$  mm Hg). Under local anesthesia (procaine HCl, 1%) a catheter was inserted into the tail artery for continuous blood pressure monitoring as well as for intermittent blood sampling for measurement of acid-base status. Body temperature was maintained at  $37 \pm 0.3^\circ C$ .

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and the animals placed in the right lateral decubitus position to minimize elevations in pelvic venous pressure.

Following these procedures, dams were administered either: (1) 70% N<sub>2</sub>-30% O<sub>2</sub>; (2) halothane (Fluothane) at concentrations of 0.4, 1, or 2% in 70% N<sub>2</sub>-30% O<sub>2</sub>; (3) pentobarbital 50 or 200 mg/kg intravenously, ventilation being continued with 70% N<sub>2</sub>-30% O<sub>2</sub>. Special attention was given to those paralyzed animals receiving no anesthesia or anesthesia in low concentrations in order to minimize discomfort. All surgical wounds were infiltrated with 1% procaine HCl and closed with sutures.

Following a 90-min experimental period, dams were decapitated and fetuses delivered via hysterotomy (Cesarean section) and immediately frozen *in amnio* in liquid nitrogen. All fetuses were frozen or blood samples collected within 10 sec of maternal sacrifice. Fetal brains were dissected, powdered, and weighed at -20°C. Perchloric acid extracts were then prepared as previously described (4). Glycolytic intermediates and high-energy compounds were measured fluorometrically with pyridine nucleotides and appropriate enzymes (4, 5).

## Results

### Behavioral Responses

To assess the depth of anesthesia induced by halothane, unrestrained term pregnant rats were examined following exposures of increasing concentrations of halothane in an air tight chamber maintained at 37°C. Fetuses delivered by Cesarean section after maternal decapitation, were observed for respiratory movements and for heart rate by EKG monitoring (Table 1).

Halothane (0.4%) did not produce surgical anesthesia, as evidenced by the presence of maternal corneal and righting reflexes as well as purposeful movements, and the majority (77%) of the fetuses breathed spontaneously. Dams exposed to 1%

halothane exhibited no response to tail pinch or righting behavior; corneal reflexes were depressed. Fetuses demonstrated spinal reflex activity but failed to revive. Dams were deeply anesthetized with 2% halothane but continued to breathe; none of the fetuses survived.

For comparison, rats receiving 50 mg/kg of pentobarbital IP lost muscle tone and exhibited rapid, shallow respirations while retaining corneal reflexes and withdrawal responses to pain. Pentobarbital, 200 mg/kg, produced maternal apnea and death. Fetuses of all barbiturate-treated animals were anesthetized and unable to be resuscitated by stimulation alone, although heart rates were similar to those of unanesthetized, decapitated dams.

### Maternal Blood Pressure

Alterations in mean arterial blood pressure were observed in pregnant rats subjected to halothane and pentobarbital (Fig. 1). The decline in blood pressure during halothane anesthesia appeared linear with increasing concentrations up to 1%, but beyond this level the severity of hypotension was not proportional to the anesthetic dose. The lowest recorded blood pressure (37 mm Hg) occurred in dams receiving 200 mg/kg of pentobarbital.

### Maternal and Fetal Blood Lactate

Halothane (0.4%) actually depressed maternal blood lactate compared to unanesthetized control animals, while higher doses of the agent led to increasing levels of the metabolite (Fig. 2). Lactate was not altered by 50 mg/kg of pentobarbital, but 200 mg/kg produced the most severe lactacidemia of any experimental group. The high maternal lactate levels during anesthesia with 2% halothane and 200 mg/kg pentobarbital were associated with significant reductions in arterial pH, indicating the existence of metabolic acidosis in these animals. Fetal blood lactate closely followed and was always

Table 1. Behavioral responses to anesthesia.

Anesthesia	Maternal			Fetal	
	Pain	Corneal	Righting	Respiration	Heart Rate
Halothane					
0.4%	+++	+++	+++	++	+++
1.0%	-	±	-	-	+++
2.0%	-	-	-	-	+++
Pentobarbital					
50 mg/kg	++	++	-	-	+++
200 mg/kg	-	-	-	-	+++

\*Term pregnant rats were exposed to increasing concentrations of halothane in air tight jars at 37°C. Other rats received pentobarbital IP. Fetuses were delivered by Cesarean section immediately following maternal decapitation.

greater than respective maternal concentrations. This lacticacidemia suggested fetal as well as maternal systemic acidosis.

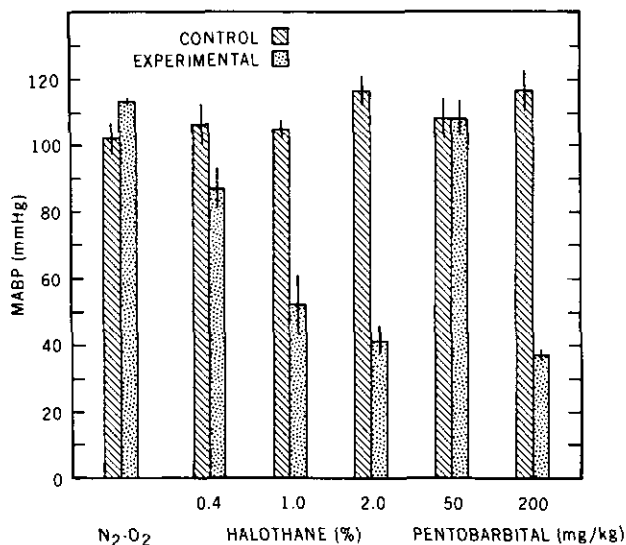


FIGURE 1. Effect of halothane and pentobarbital on mean arterial blood pressure in pregnant rats. Term pregnant rats were paralyzed and ventilated with either 70% N<sub>2</sub>-30% O<sub>2</sub> (control) or halothane in 70% N<sub>2</sub>-30% O<sub>2</sub>. Dams receiving pentobarbital (IV) were ventilated with 70% N<sub>2</sub>-30% O<sub>2</sub>. Control values (mm Hg) represent means of three animals prior to anesthetic exposure; experimental values are means of the same animals 90 min later. Vertical lines denote  $\pm 1$  S.E.M.

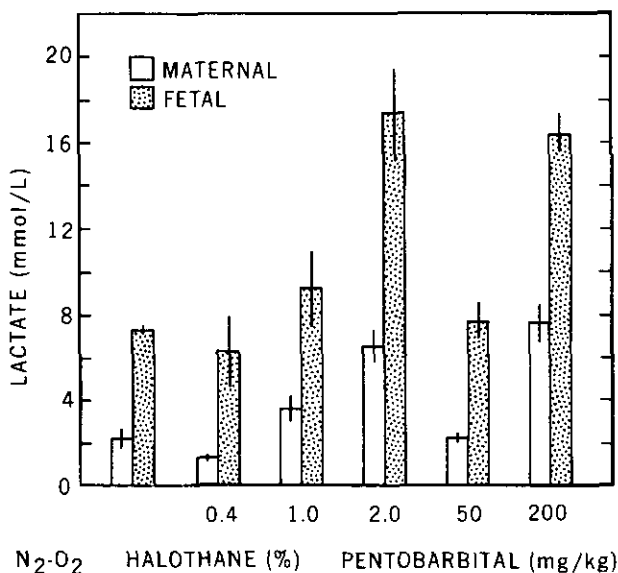


FIGURE 2. Effect of halothane and pentobarbital on maternal and fetal blood lactate. Pregnant rats were exposed to anesthesia as described in Fig. 1. Blood samples were collected following 90 min of anesthesia. Values, expressed as mmole/l., represent means of three animals. Vertical lines denote  $\pm 1$  SEM.

## Glycolytic Intermediates and High-Energy Reserves in Fetal Brain

Cerebral oxidative metabolism of fetuses of halothane-treated dams was adversely influenced by increasing concentrations of the anesthetic agent (Fig. 3). Halothane (0.4%) had no effect on fetal brain constituents when compared to unanesthetized, paralyzed animals. Halothane (1%) led to a doubling in lactate levels with a disproportionate increase in pyruvate, such that the lactate/pyruvate ratio was increased by 50%. Phosphocreatine was reduced by 39%, whereas ATP remained within normal limits. Halothane (2%) was associated with further elevations in lactate, but pyruvate actually declined; the resultant lactate/pyruvate ratio was 10-fold higher than the control value. The energy state of the brain was also disrupted by 2% halothane, with near total exhaustion of phosphocreatine and a 43% reduction in ATP. ADP and AMP were increased in concentrations proportionate to the declines in ATP.

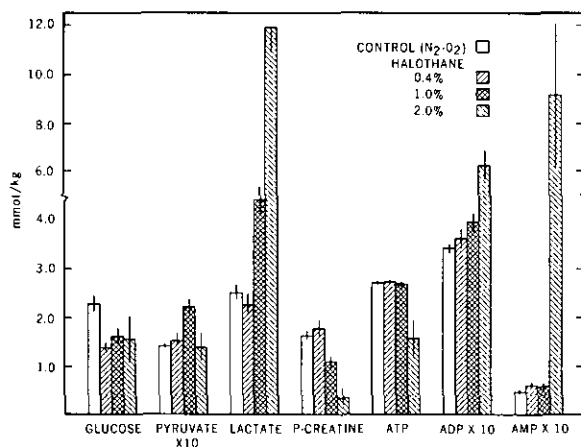


FIGURE 3. Cerebral glycolytic intermediates and high-energy compounds in fetuses of halothane anesthetized pregnant rats. Control levels are those obtained in fetuses of unanesthetized, paralyzed dams. Values, expressed as mmole/kg brain wet weight, represent means of nine animals. Vertical lines denote  $\pm 1$  SEM.

Like 0.4% halothane, pentobarbital (50 mg/kg) was without deleterious effect on oxidative metabolism in fetal brain (Fig. 4). Increasing the anesthetic dose to 200 mg/kg led to alterations in cerebral constituents similar to those observed in fetuses exposed to 1% halothane. Thus, the lactate/pyruvate ratio was 236% of control paralyzed animals and phosphocreatine reduced by 47%. ATP levels were not different with only slight elevations in ADP and AMP. These disturbances in cerebral metabolism were not as severe as those

observed in fetuses subjected to 2% halothane even though the pentobarbital treated dams were rendered the most hypotensive of any anesthetic group.

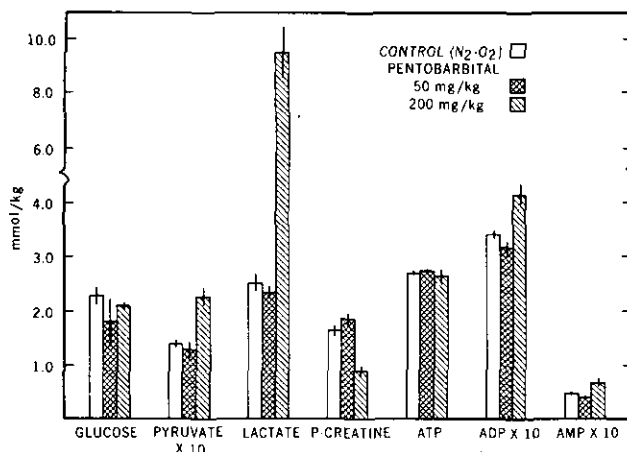


FIGURE 4. Cerebral glycolytic intermediates and high-energy compounds in fetuses of pentobarbital anesthetized pregnant rats. Control levels are those obtained in fetuses of unanesthetized, paralyzed animals. Values, expressed as mmole/kg brain wet weight, represent means of nine animals. Vertical lines denote  $\pm 1$  SEM.

## Discussion

In the present study, anesthesia was associated with significant alterations in maternal blood pressure and in acid-base balance. The well-documented maternal hypotension during halothane anesthesia (6-8) was associated with elevated blood lactate, which rose steadily as the maternal blood pressure fell. The hypotension undoubtedly produced tissue ischemia in the dam and a shift to anaerobic glycolysis resulting in lactacidemia. Pentobarbital (200 mg/kg) also led to maternal hypotension and to lactacidemia to a degree similar to that observed with 2% halothane. Fetal lactate concentrations paralleled corresponding levels in dams. The origin of the fetal lactacidemia was unknown, but possibilities included passage from the maternal to the fetal circulation, placental anaerobiosis or endogenous production secondary to fetal hypoxemia. Whatever the source, the lactacidemia suggested fetal as well as maternal systemic acidosis (see below).

Fetuses of dams exposed to the lowest concentrations of halothane (0.4%) and pentobarbital (50 mg/kg) exhibited levels of cerebral glycolytic intermediates and high-energy compounds which were comparable to those of fetuses from unanesthetized, paralyzed dams. Concentrations of halothane greater than 0.4% were associated with major disturbances in glycolytic intermediates and the energy state of the fetal brain. At these levels of

anesthesia, arterial blood pressures of dams were reduced by at least 50%. Maternal hypotension, induced by halothane, is known to lead to reduced uterine blood flow and diminished placental diffusion of oxygen and carbon dioxide, resulting in fetal hypoxemia and acidosis (9-11). Systemic fetal hypoxia would also account for the elevated concentrations of blood lactate, possibly aggravated by reduced placental clearance of the organic acid. Halothane may also affect the fetus directly by producing fetal bradycardia and hypotension, although similar disturbances in cardiovascular hemodynamics are known to result from perinatal systemic hypoxia (12-14).

The known differential effects of halothane and barbiturates on brain metabolism may, at least in part, explain the present findings in halothane and pentobarbital anesthetized fetuses. Halothane (2%) and pentobarbital (200 mg/kg) led to near identical reductions in maternal arterial blood pressure and to increases in maternal and fetal lactate concentrations, alterations which suggest similar degrees of fetal hypoxemia and/or acidosis. In fetal brain, deep halothane anesthesia was associated with a 10-fold increase in the lactate/pyruvate ratio and a decline in ATP with proportionate increases in ADP and AMP. In contrast, profound pentobarbital anesthesia produced only a 2-fold elevation in the lactate/pyruvate ratio with no alteration in ATP. Thus, pentobarbital served to preserve an optimal cerebral energy state in the presence of systemic hypoxia. Barbiturates are known to protect fetal and newborn animals against hypoxia, both by prolonging survival and by reducing or preventing subsequent development of structural brain damage (15-17). Possibly, the cerebral metabolic influence of barbiturates observed in the present study aids in protecting the hypoxic fetus from long-term neurological damage, an effect apparently not shared by maternally administered halothane.

This study was supported by Public Health Service Grant HD-09109 from the National Institute of Child Health and Human Development.

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